REMARKS

Reconsideration of the application is respectfully requested. Claims 7 and 11 have been amended to specify administration of a unitary oral dosage form. Support for this amendment is found in the specification at, for example, page 3, paragraph 7. No new matter has been added. Claims 2-11 and 16-23 are pending and at issue.

Provisional Double Patenting Rejections

Claims 2-11 and 16-23 have been provisionally rejected under the judicially created doctrine of obviousness-type double patenting over claims 1-10 of co-pending U.S. Patent Application No. 10/861,239, and over claims 12-18 of co-pending U.S. Patent Application No. 10/925,783. Submitted herewith are terminal disclaimers over U.S. Patent Application Nos. 10/861,239 and 10/925,783. Accordingly, applicants respectfully request withdrawal of these provisional rejections.

Rejections Under 35 U.S.C. § 102(b)

Claims 2, 3, 7-11, 22, and 23 have been rejected under 35 U.S.C. § 102(b) as anticipated by Cooper et al., *Clinical Pharmacology & Therapeutics*, PII-9 (February 1993) ("Cooper"). Additionally, claims 2, 3, 5, 7-11, 22, and 23 have been rejected under 35 U.S.C. § 102(b) as anticipated by Dionne, *J. Oral Maxillofac. Surg.*, 57:673-678 (1999) ("Dionne").

These rejections are respectfully traversed, and reconsideration is requested.

Cooper discloses a clinical study in which patient groups experiencing pain due to surgical removal of impacted teeth were administered one of three different combinations of capsules: (1) two ibuprofen capsules and one oxycodone capsule; (2) two ibuprofen capsules and one placebo capsule; or (3) three placebo capsules. *See* Specification at p. 3, ¶ 5. In the Cooper study, patients were not administered a unitary dosage form containing a combination of active ingredients (i.e., oxycodone

and ibuprofen), as required by the present claims. Therefore, Cooper, does not anticipate claims 2, 3, 7-11, 22, and 23.

Dionne fails to disclose administration of a unitary dosage form as well. Rather, Dionne discloses a clinical study in which patient groups experiencing pain due to surgical removal of impacted teeth were administered one of four different treatments: (1) one 400 mg ibuprofen dosage form; (2) one 400 mg ibuprofen dosage form and one 2.5 mg oxycodone dosage form; (3) one 400 mg ibuprofen dosage form and one 5 mg oxycodone dosage form; or (4) one 400 mg ibuprofen dosage form and one 10 mg oxycodone dosage form. *See* Dionne at p. 674, right column, first paragraph. In the Dionne study, patients were not administered a single dosage form containing a combination of active ingredients (i.e., oxycodone and ibuprofen), as required by the present claims. In fact, Dionne expressly states that the "therapeutic advantage to oxycodone combinations is the ability to administer two tablets, a dose of 10 mg oxycodone, to produce greater analgesia." Dionne at p. 674, left column, first full paragraph (emphasis added). Therefore, Dionne does not anticipate claims 2, 3, 5, 7-11, 22, and 23.

Accordingly, applicants respectfully request withdrawal of these rejections.

Rejections Under 35 U.S.C. § 103(a)

Claims 2-11 and 16-23 have been rejected under 35 U.S.C. § 103(a) as obvious over Baker et al. (U.S. Patent No. 4,569,937) ("Baker"), Cooper, and Dionne. According to the Examiner, it would have been obvious to use a unitary oral dosage form (as taught by Baker) comprising the claimed amounts of oxycodone and ibuprofen (as taught by Cooper and Dionne) for treating acute pain.

The rejection is respectfully traversed, and reconsideration is requested.

To establish obviousness, "the prior art as a whole must 'suggest the desirability'" of combining the references. *In re Fulton*, 391 F.3d 1195, 1200 (Fed. Cir. 2004) (citing *In re Beattie*,

974 F.2d 1309, 1311 (Fed. Cir. 1992). When the combination involves a trade-off (i.e., where the motivating benefit of the combination comes at the expense of another benefit), "the benefits, both lost and gained, should be weighed against one another." *Winner Int'l Royalty Corp. v. Wang*, 202 F.3d 1340, 1349 (Fed. Cir. 2000). In the context of an obviousness determination, "[t]rade-offs often concern what is feasible, not what is, on balance, desirable. Motivation to combine requires the latter." *Id.*

Here, the prior art as a whole does not suggest the desirability of a unitary dosage form containing about 5-10 mg oxycodone and about 350-500 mg ibuprofen, as recited in the present claims. On the contrary, the prior art suggests that this combination is undesirable in view of a significant benefit-to-risk relationship recognized and described in each cited reference. This relationship balances the benefit of increasing the amounts of active ingredient to potentially provide a greater analgesic effect with the risk of increasing the incidence of adverse events brought on by the increase in active ingredient.

Dionne discloses that co-administration of oxycodone and ibuprofen produces undesirable results. In fact, Dionne teaches away from this combination by concluding that, depending on the amount of oxycodone, the combination either has no greater analgesic effect than ibuprofen alone, or its risks outweigh its benefits. In the Dionne study, patients were treated with one 400 mg ibuprofen dosage form administered either alone or with one 2.5, 5, or 10 mg oxycodone dosage form. Dionne at p. 676. Dionne found that administration of a 5 mg oxycodone dosage form with a 400 mg ibuprofen dosage form was no more effective at relieving pain than administration of a 400 mg ibuprofen dosage form alone.

> [T]he combination of [400 mg] ibuprofen with 5 mg oxycodone ... did not result in any detectable additive effects on any of the four analgesic scales used at any point.

Dionne at p. 676, left column, first paragraph. Accordingly, Dionne would not have motivated one of

ordinary skill in the art to combine 5 mg oxycodone and 400 mg ibuprofen in a unitary dosage form because such a combination would not have been expected to be any more effective than 400 mg ibuprofen alone.

Cooper also discloses a study involving co-administration of a 5 mg oxycodone dosage form with a 400 mg ibuprofen dosage form, and concludes that this combination causes a high incidence of adverse events. *See* Cooper ("The combination [of 5 mg oxycodone and 400 mg ibuprofen] had the highest incidence of side effects."). Thus, one of ordinary skill would have been further discouraged from using 5 mg oxycodone and 400 mg ibuprofen in a unitary dosage form because not only would such a combination be expected to be no more effective than 400 mg ibuprofen alone, but it would produce a high incidence of side effects.

Dionne also discloses that co-administration of a 10 mg oxycodone dosage form and a 400 mg ibuprofen dosage form is undesirable because the risk of side effects due to this combination strongly outweighs its potential benefits. In the Dionne study, the patients who received this treatment experienced only a marginal additive analgesic effect that was confined to the initial two hours following drug administration, and was achieved at the expense of a significant increase in adverse events. Dionne at p. 676, right column, first full paragraph. Specifically, these patients suffered from a high incidence of central nervous system-mediated adverse events (an approximate twofold increase), which was directly attributable to the additional opioid (oxycodone). Dionne at p. 676, right column, first full paragraph. Dionne reports that 84% (26 out of 31) of the patients who received this combination suffered from adverse events (e.g., drowsiness, nausea, vomiting, dizziness, etc.), as opposed to only 38% (11 out of 29) of the patients who received 400 mg ibuprofen alone. Dionne at p. 676, bottom table. According to Dionne, the 10 mg oxycodone combination was of "questionable therapeutic benefit" in view of this substantial increase in side effects. Dionne at p. 676 second full paragraph. Thus, Dionne teaches away from co-administration of oxycodone and

ibuprofen by concluding that this combination produces undesirable results and by endorsing alternative approaches.

To reduce the serious risk of side effects, Dionne instead advocates administration of a non-steroidal anti-inflammatory drug (NSAID), such as ibuprofen, in the absence of (or at least separately from) an opioid for the treatment of pain. For example, before the offset of local anesthesia, Dionne suggests administering an NSAID with or without a long-acting local anesthetic in order to achieve a more favorable benefit-to-risk relationship than that afforded by concurrent administration of an NSAID-opioid combination. *See* Dionne at p. 677, first paragraph. Dionne further states that optimization of the benefit-to-risk relationship associated with administering an NSAID-opioid combination "can be best achieved by only administering the opioid to patients who need the additional analgesic benefit and titrating the dose on the basis of side effects." Dionne at p. 677, right column, last paragraph to p. 678, left column, first paragraph.

Therefore, at best, Dionne provides motivation to administer NSAID-opioid combinations in separate dosage forms only (i.e., not as a unitary dosage form) in order to better control the incidence of adverse events in a patient-specific manner, and to avoid prompting adverse events unnecessarily. *See* Dionne at p. 677, left column, first paragraph.

Baker, too, appreciates the risk of adverse events caused by administration of analgesics.

> More active analgesic combinations are in constant demand because they offer the attractive possibility of relieving pain with reduced dosages, thereby diminishing the expected side effects and toxicity that would result from the otherwise required higher dosages.

Baker at col. 1, lines 13-17. These reduced dosages are apparent in Baker's exemplified compositions. For instance, the composition containing the greatest amounts of oxycodone and ibuprofen is disclosed in Example 5 and combines 5.0 mg oxycodone with 300.0 mg ibuprofen. *See* Baker at col. 5, lines 6-19 (Example 5). These are the maximum dosage amounts of oxycodone and

ibuprofen exemplified in Baker. This reference does not disclose a unitary dosage form comprising about 5-10 mg oxycodone and about 350-500 mg ibuprofen, as presently claimed.

Increasing the amount of active ingredients in the Baker compositions to the levels presently claimed would be contrary to Baker's stated advantage of providing a reduced dosage of analgesic. Further, by attempting to provide reduced dosages of oxycodone and ibuprofen and by not exemplifying, disclosing, or even suggesting compositions comprising about 5-10 mg oxycodone and about 350-500 mg ibuprofen, Baker suggests that this combination (as presently claimed) is undesirable.

Additionally, Baker does not suggest the use of compositions containing more than 5.0 mg of oxycodone and/or more than 300.0 mg of ibuprofen since increased amounts of the active ingredients could unnecessarily prompt an increase in adverse events. *See*, for example, Baker at col. 3, lines 28-33. Thus, a person of ordinary skill in the art would not have been motivated to use a composition comprising 5 mg of oxycodone and 400 mg of ibuprofen (an amount of ibuprofen greater than the maximum 300.0 mg exemplified in Baker) for the treatment of acute pain because the additional ibuprofen would not only be unnecessary, but would also present a risk of increased adverse events (as found by Dionne and Cooper) by exposing the patient to additional analgesic. Likewise, one of ordinary skill would not have been motivated to use compositions comprising about 5-10 mg oxycodone and about 350-500 mg ibuprofen because these compositions include even higher dosages of analgesic, and thus would have been expected to provoke additional adverse events.

In summary, the prior art as a whole suggests that the presently claimed combination would be undesirable. One of ordinary skill, upon reading the prior art, would have considered the risk of increased and unnecessary adverse events to have outweighed the potential benefit of increased analgesic effect (which was not observed with the 5 mg oxycodone dosage form, as reported by Dionne). This risk is recognized and appreciated in all three cited references, and especially in

Dionne, which assesses this trade-off in detail and plainly concludes that the benefit-to-risk relationship weighs against co-administration of the two analgesics.

Additionally, while assessing the benefit-to-risk relationship, one of ordinary skill would also have considered the intended purpose of the composition. In each cited reference, the combination of oxycodone and ibuprofen was administered for the treatment of pain - i.e., to improve the comfort of the patient. A significant increase in side effects (e.g., drowsiness, nausea, vomiting, dizziness, etc.) would only worsen a patient's level of comfort and would thus be directly contrary to the intended purpose of such treatment. Accordingly, the risks would further outweigh the potential benefit.

Nevertheless, despite the discouragement of the prior art, the present inventors have surprisingly discovered that a unitary dosage form containing about 5-10 mg of oxycodone and about 350-500 mg of ibuprofen administered for the treatment of acute pain or acute postoperative pain not only produces an additive analgesic effect with an acceptable level of adverse events, but also has the unexpected advantage of accelerating the onset of pain relief. These unexpected results are illustrated in Example 8 (p. 22, ¶ 71 to p. 24) and in Figure 4, which show that the maximum ibuprofen plasma concentration occurs earlier upon administration of the presently claimed unitary dosage form than co-administration of separate oxycodone and ibuprofen dosage forms. Specifically, the amount of time required to reach maximum ibuprofen plasma concentration (T_{max}) for the unitary dosage form was 1.4 hours, whereas the T_{max} value for the separate dosage forms was 2.2 hours. Specification at p. 23, Table 1. The present inventors have also found that the claimed unitary dosage form results in a statistically significant earlier onset of pain relief than administration of either ingredient alone. Specification at p. 5, ¶ 11.

Additionally, Example 10 (p. 32, ¶ 90) and Figures 12 and 13 show that the presently claimed unitary dosage form produces a faster oxycodone dissolution rate and thus allows for more rapid absorption of oxycodone. As shown in Figure 12, for example, a tablet comprising 5 mg

oxycodone and 400 mg ibuprofen dissolves significantly faster than either a tablet of 5 mg oxycodone alone or a combination of three tablets (one containing 5 mg oxycodone and two containing 200 mg each of ibuprofen). Thus, administration of the presently claimed unitary dosage form provides an analgesic effect much more quickly than the concurrent administration of the individual active ingredients. Similarly, Figure 13 shows that significantly more oxycodone was absorbed by Caco-2 cells 60 minutes after administration of the 5 mg oxycodone / 400 mg ibuprofen tablet when compared with the amount absorbed after co-administration of the three separate tablets.

In view of the foregoing, Cooper, Dionne, and Baker would not have motivated one of ordinary skill in the art to combine oxycodone and ibuprofen in a unitary dosage form comprising about 5-10 mg oxycodone and about 350-500 mg ibuprofen. Furthermore, the advantageous results achieved by administering a unitary dosage form containing the claimed amounts of each active ingredient were surprising and unexpected. Therefore, because claims 2-11 and 16-23 are not obvious over Cooper, Dionne, and Baker, this rejection should be withdrawn.

Conclusion

In view of the above amendments and remarks, it is respectfully requested that the application be reconsidered and that all pending claims be allowed and the case passed to issue.

If there are any other issues remaining, which the Examiner believes could be resolved through either a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at the telephone number indicated below.

Dated: December 2, 2005

Respectfully submitted,

By_____

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